Exhibit 1

Expert Rebuttal Declaration of

James M. Cantor, PhD

Poe et al v. Drummond et al

Northern District of Oklahoma

Table of Contents

1. I have received and reviewed the rebuttal declarations of Drs. Adkins, Antommaria, Janssen, and Turban. The brief period available for response does not permit corrections to each of their errors with the depth or breadth they merit. Because the most numerous and substantial of those errors represent individual instances of contradicting the principles of evidence-based medicine, rejecting the scientific method, and failing to address the errors already identified in my initial declaration, my following comments address the most glaring examples of violating those principles.

2. My initial declaration included sections (Cantor decl, ¶¶ 259–304) identifying numerous errors I identified in the plaintiffs' opening memorandum and each of their experts' declarations. With some exceptions in Dr. Antommaria's rebuttal, the rebuttal declarations did not contest that these claims were indeed erroneous. Instead, the rebuttals consisted mostly of reiterating their original errors, entirely ignoring documentation of their mistakes.

I. Clinical decision-making consists of analyzing the risk-to-benefit ratio given uncertainty, and arguments are invalid when missing analysis of risk or benefit or uncertainty.

3. Clinical decision-making is based on assessing the risk-to-benefit ratio given the uncertainties of the alternatives. That is, treatments with low risk of harm can be justified by low quality evidence, but treatments with high risk of harm require high quality evidence of benefit. In the present context, psychotherapy poses very low risk of harm (if any at all), whereas the risks of medicalization are objectively high. The evidence of potential benefits of transition is of low quality and is highly subjective. The diagnoses of purely medical conditions (such as precocious puberty and disorders of sexual development) can be made with very high accuracy and on the basis of objective, physical testing, but the diagnosis of gender dysphoria is highly uncertain, based on ambiguous features with no objective means of verification.

4. The plaintiffs' experts demonstrate awareness of the roles of these three factors—risk, benefit, and uncertainty—but repeatedly evade their proportionality, providing no risk-to-benefit analyses. Their arguments repeatedly consist of naming an exception, but ignoring that the conditions which can (sometimes) permit such an exception are absent regarding gender dysphoria. That is, naming an exception wherein a high-risk procedure is acceptable is irrelevant when it ignores that the exception applies only to conditions diagnosed with high certainty (whereas the diagnosis of gender dysphoria is quite uncertain). Naming an exception wherein low quality evidence is acceptable is irrelevant when it ignores that the exception applies only to low-risk interventions (whereas medicalized transition includes very high-risk interventions).

5. In the plaintiffs' experts' materials, Dr. Antommaria claimed "None of these reports or statements meets the standards to which the Defendants' experts hold the Endocrine Society's and WPATH's clinical practice guidelines" (Antommaria rebuttal decl, ¶32). Because psychotherapy poses so much less risk than does medicalized transition, however, it does not hold the same burden of evidence as medicalized transition: It is the medicalization that holds the burden of proof to demonstrate it provides greater benefit to justify its greater harms to objectively healthy and functioning tissue. This represents an instance of the central medical ethic of *Do no harm.* Dr. Antommaria claimed "it does not appear from the summary that a systematic review of the literature was conducted in the formulation of every recommendation" (¶32); however, as explicated in my initial report, WPATH's review did not include safety *at all*, and the Endocrine Society review did not include puberty blockers *at all* (Table 1, Cantor decl, p. 34).

II. The plaintiffs' experts misrepresent and minimize the role of the Systematic Review process and engage in the very cherry-picking and biased evaluation of evidence that the process was developed to prevent.

6. Especially with highly contested research findings, it has long been common for authors to provide analyses that are highly biased, such as by (1) engaging in cherry-picking, citing only the studies, or only the parts of studies, that seem to support their view, or (2) by holding studies to a higher or lower standard according to whether they support or contradict the authors' view. To address that problem, the process of *systematic review* was developed, as detailed in my initial declaration: The steps of systematic review, including explicit disclosure of all studies, of the inclusion/exclusion criteria, and so on, all minimize opportunities for such biases to affect conclusions.

7. These features of systematic reviews are reflected by the National Institutes of Health (NIH) and the National Academy of Sciences. From the NIH Office of Research Services:[1]

> According to Cook, Mulrow, and Haynes, "systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their subjects. Systematic reviews synthesize the results of multiple primary investigations by *using strategies that limit bias and random error*….These strategies include a comprehensive search of multiple databases to identify potentially relevant articles and the use of *explicit, reproducible criteria in the selection of articles* for inclusion and review. Primary research designs and study characteristics are appraised, data are synthesized and results are interpreted.[2] [Italics added.]

The NIH National Heart, Lung, & Blood Institute summarizes the NAS Institute of Medicine definition of systematic review as:[3]

> In 2011, the Institute of Medicine (IOM) defined a systematic evidence review as "a scientific investigation that focuses on a specific question and uses explicit, prespecified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. It may include a quantitative synthesis (meta-analysis), depending on the available data." Systematic evidence reviews of comparative effectiveness research to learn what is known and not known about the potential benefits and harms of alternative drugs, devices, and other healthcare services *provides the best evidence to inform clinical decisions.* [Italics added]

[1] Available from https://www.nihlibrary.nih.gov/services/systematic-review-service
[2] Cook, D. J., Mulrow, C. D., & Haynes, R. B. (1997). Systematic reviews: Synthesis of best evidence for clinical decisions. *Annals of Internal Medicine, 126,* 376–80.
[3] Available from https://www.nhlbi.nih.gov/node/80397

> The NHLBI appoints expert panels to conduct systematic evidence reviews to enable clinical practice guidelines development. An expert panel is a committee of unpaid experts. The chair and members are chosen mainly for their scientific and clinical expertise. *Excluded are individuals with clear financial conflicts and those whose professional or intellectual bias would diminish the credibility of the review.* [Italics added.]

Factors that are considered by systematic reviews in evaluating the quality of research evidence are provided by the PRISMA reporting guidelines. A copy of those guidelines is appended to the present rebuttal declaration.

8. The profundity of the plaintiffs' experts' misrepresentation of the systematic review process is illustrated by comparing either of these NIH sources (or the peer-reviewed sources cited in my original declaration) indicating the purpose of systematic review to be to provide unbiased conclusions, with the description provided by Dr. Turban: "all a 'systematic review' means is that the authors of the reports pre-defined the search terms they used" (Turban rebuttal decl, ¶5). Somehow, in Dr. Turban's view, the prevention of bias, prevention of cherry-picking, and use of universal reporting standards to ensure all studies are evaluated on equal footing, did not merit mention. The plaintiffs' experts' opinions do not survive the application of these universal standards of science.

9. In claiming that pre-defined search terms is all that 'systematic review' means, Dr. Turban cited a single source: https://guides.library.harvard.edu/meta-analysis/gettingstarted. What that source actually says, however, is:

> A systematic review is guided filtering and synthesis of *all available evidence* addressing a specific, focused research question, generally about a specific intervention or exposure. *The use of standardized, systematic methods and pre-selected eligibility criteria reduce the risk of bias in identifying, selecting and analyzing relevant studies.* A well-designed systematic review includes clear objectives, pre-selected criteria for identifying eligible studies, an explicit methodology, a thorough and reproducible search of the literature, an assessment of the validity or risk of bias of each included study, and a systematic synthesis, analysis and presentation of the findings of the included studies. A systematic review may include a meta-analysis. [Italics added.]

Several observations apply: (1) As the italicized text shows, Dr. Turban's source describes the purpose of systematic reviews the same way I have: to minimize bias in selecting and evaluating the studies in the research literature. (2) Dr. Turban either misrepresents or misunderstands his source. It does not refer to "search terms" as one might enter into a Google search to ensure one has gotten all the relevant "hits." Rather, it refers to the *inclusion/exclusion criteria* used for deciding which of those studies get entered into versus from excluded from the systematic review: That step is what prevents the cherry-picking. The inclusion/exclusion criteria are applied to the results of applying search terms to research databases.

III. In minimizing the importance of systematic review, the plaintiffs' experts engage in the very biases the process is designed to prevent, holding studies to higher versus lower standards according to whether they support or challenge their opinions. This includes accepting or rejecting pre-DSM-5 studies that challenge versus (seem to) favor them.

10. Dr. Turban claimed that "the primary advantage to a systematic review would be to identity research publications that had not previously been identified in this discussion" (Turban rebuttal, ¶5). That claim ignores the actual advantage, as noted even by Dr. Turban's own source: Systematic review prevents the very biases on which the plaintiffs' experts' arguments rely. The so-called "publications that had not previously been identified" are the very studies that disconfirm Dr. Turban's opinions. All this is entirely consistent with the contents of my initial declaration, which exhaustively listed all available outcomes studies (Cantor decl, ¶¶178–201), whereas the plaintiffs' experts cherry-picked only those studies seeming to support them and omitted the failures to replicate those results, and which demonstrate the unreliability of their conclusion.

11. As noted already, the systematic review process includes making assessment criteria explicit and holding them constant across all research studies. The plaintiffs' experts do the

reverse. My declaration included all follow-up studies of prepubescent children, which demonstrated unanimously that the large majority of them desist in feeling gender dysphoric by puberty (Cantor decl, Section IX.B.1). The plaintiffs' experts repeatedly argued these studies to be outdated because they did not use DSM-5 diagnostic criteria and included too broad a sample. In direct contradiction of that same standard, they repeatedly cite and support multiple studies that did not use DSM-5 criteria or, in an even greater contradiction, survey studies that use no DSM diagnoses at all, thus including samples even broader than in the studies they reject. Examples include:

- de Vries et al. (2011) gathered its samples before the DSM-5 (published in 2012) and did not use its diagnostic criteria.
- de Vries et al. (2014) was a follow-up of the same individuals as de Vries et al. (2011), gathered before the DSM-5 criteria.
- Olson et al. (2022) employed no DSM or other diagnosis at all.
- Tordoff et al. (2022) employed no DSM or other diagnosis at all, instead including any patient who completed the telephone intake and in-person appointments.
- Achille et al. (2020) did not employ DSM or other diagnosis, instead providing treatments following Endocrine Society and WPATH guidelines, which, in turn, require no DSM or other diagnosis.

IV. The plaintiffs' experts evade the central point: Endorsement of medicalized transition is limited to committees and associations that failed to conduct systematic reviews of safety and evidence, to which the experts respond by merely repeating the conclusions of those groups while ignoring the conclusions by the groups that *did* conduct such reviews.

12. My initial declaration listed on a single table (Table 1, Cantor decl, p. 34) every study identified by every systematic review, including the Endocrine Society, WPATH (published as Baker et al., 2021), and the American Academy of Pediatrics. As noted there and in the body of my declaration, WPATH included zero studies of safety, the Endocrine Society included zero studies of puberty blockers, and AAP conducted no systematic review at all. None of the

plaintiffs' experts contested this, nor indicated that I left out any study of safety of effectiveness. The counterargument they provide, however, simply restates the endorsements from those groups, ignoring that those endorsements have no scientific basis.

13. Whereas I list the basis of the committees' decisions, the plaintiffs' experts respond only by reiterating these committees' decisions. This, however, is exactly how medical mismanagement occurs: It is not possible to detect when a committee is failing to apply the relevant science and principles when the committee's actions are used as evidence of the principles, instead of using the principles as the basis for evaluating the committee's decisions.

14. This very same error applies to Dr. Antommaria's lack of awareness of the meaning of experimental. NIH maintains ClinicalTrials.gov, a U.S. government website and database of clinical research studies for scientists, health care professionals, and the public. Its section for "Study Basics" includes a glossary, which provides the entries below, defining "experimental" the same way as appears in my initial declaration: Experiments test treatments by comparing two groups (or "arms"), one that receives the treatment and one that does not.[4] Because medicalized transition has not yet been tested with a two-group design, it has not yet passed the experimental stage. (The glossary also includes the "active comparator" option also appearing in my initial declaration; Cantor decl, ¶¶ 52–53.)

> **Arm**
> A group or subgroup of participants in a clinical trial that receives a specific intervention/treatment, or no intervention, according to the trial's protocol.
>
> **Arm type**
> A general description of the clinical trial arm. It identifies the role of the intervention that participants receive. Types of arms include experimental arm, active comparator arm, placebo comparator arm, sham comparator arm, and no intervention arm.

[4] Available from https://clinicaltrials.gov/study-basics/glossary

> **Experimental arm**
> An arm type in which a group of participants receives the intervention/treatment that is the focus of the clinical trial.
>
> **No intervention arm**
> An arm type in which a group of participants does not receive any intervention/ treatment during the clinical trial.
>
> **Active comparator arm**
> An arm type in which a group of participants receives an intervention/treatment considered to be effective (or active) by health care providers.

The NIH Grants and Funding website page also provides the definition of experimental for investigations not pertaining to treatment outcomes, and it again indicates this to mean designs with two (or more) groups:[5]

> **Basic Experimental Studies with Humans**
> Studies that prospectively assign human participants to conditions (i.e., experimentally manipulate independent variables) and that assess biomedical or behavioral outcomes in humans for the purpose of understanding the fundamental aspects of phenomena without specific application towards processes or products in mind.

15. As noted in my initial declaration and to which there has been no challenge, the highest level research design yet applied to studying treatment outcomes is the cohort study (Cantor decl, section III.D). In these studies, a single group of individuals was assessed before and again after undergoing medicalized transition. Because this design does not include a second group (i.e., no control group or "arm"), it does not represent an experiment. Rather, this represents a "quasi-experimental" design, specifically, it is the "pre-post without control" design. In clinical research, there exist 11 quasi-experimental designs, which comprise a hierarchy according to their relative ability to establish causality, and, of these, the pre-post without control design represents the second to *least* able to establish causality (Harris et al., 2006).

16. Because they do not use randomization, quasi-experimental designs are subject to

[5] Available from https://grants.nih.gov/policy/clinical-trials/glossary-ct.htm#BasicExperimentalStudieswithHumans

nine different threats to their internal validity (Shadish et al., 2002). Of these, four are pertinent to the cohort studies of minors undergoing medicalized transition:

- Confounding (psychotherapy occurring at the same time as medicalized transition, leaving unknown which contributed to any changes detected)
- Maturation (natural development during which improvement would have happened even without transition)
- Regression to the mean (when people are selected for having extreme scores on fluctuating features, such as emotional distress, the group average is less extreme upon retest due to the fluctuation rather than the intervention)
- Drop-outs (people not benefiting over time drop out, leaving only the people who are improving)

Because the existing studies of transition are not experiments, it is not possible to know which, or all, of these might be responsible for the changes reported (of the subset of studies that found changes in the first place).

17. Dr. Antommaria also obfuscates the meaning of "experimental" (in this context, being the status of a conclusion) and of "RCT's" (a research design capable of demonstrating which factors cause which factors instead of merely correlating with each other) (Antommaria rebuttal decl, ¶ 31). Dr. Antommaria claimed:

> Finally, some of the Defendants' experts emphasize that these countries limit the provision of gender-affirming medical care to research protocols without acknowledging that this research need not be RCT. Dr. Cantor, for example, claims "Dr. Antommaria's other argument against RCTs is his belief that 'A randomized trial is unlikely to enroll enough participants.' That belief is also untenable. Healthcare systems of *entire countries* throughout Europe are limiting *all* medicalized transition to minors to research studies (298, reference omitted, italics in original)." He provides no evidence that these studies will be RCT and in fact some countries have explicitly stated that this will not be the case. For example, the Swedish NBHW states, "To ensure that new knowledge is gathered, the NBHW further deems that treatment with GnRH-analogues and sex hormones for young people should be provided within a research context, which does not necessarily imply the use of randomized controlled trials (RCTs)."

18. This is a false dilemma: Dr. Antommaria originally argued that it would not be possible to conduct RCTs, due to the difficulties he predicted in recruiting enough volunteers to participate. I pointed out that such a fear was unfounded because in several countries

participating in a research study is the only way to undergo medicalized transition. That Sweden (in Dr. Antommaria's example above) will permit non-RCT research, if scientifically needed, while researchers climb each step of the levels of evidence does not change this. It is in the American context, wherein medicalized transition is readily available to anyone outside of any systematic research protocol at all, that makes participation in research less likely.

V. Documentation updates.

19. After the submission of my original declaration, the American Academy of Pediatrics (AAP) announced that it will now be commissioning a systematic review of the evidence.[6] That announcement was widely covered by the mainstream press. *The Wall Street Journal*[7] indicated the AAP review will be conducted externally, which would be consistent with the systematic review process outlined in my initial declaration, including the methods for avoiding conflicts of interest. In *The New York Times*,[8] Dr. Gordon Guyatt referred to AAP's endorsement of medical transition before conducting such a review as "very clearly putting the cart before the horse," and he added that:

> Based on previous systematic reviews, Dr. Guyatt said, the A.A.P.'s report will most likely find low-quality evidence for pediatric gender care. "The policies of the Europeans are much more aligned with the evidence than are the Americans'," he said.
>
> In June, England's National Health Service announced[9] that it would restrict the use of puberty blockers to clinical trials because "there is not enough evidence to support their safety or clinical effectiveness as a routinely available treatment." Last year, Sweden's national health care oversight body similarly determined[10] that, on the basis of its systematic review, "the risks of puberty-inhibiting and gender-

[6] Available from https://publications.aap.org/aapnews/news/25340/AAP-reaffirms-gender-affirming-care-policy?autologincheck=redirected
[7] Available from https://www.wsj.com/articles/doctors-group-to-examine-guidelines-for-treatment-of-transgender-youths-dbe98caa?mod=hp_lead_pos3
[8] Available from https://www.nytimes.com/2023/08/03/health/aap-gender-affirming-care-evidence-review.html?searchResultPosition=3
[9] *The New York Times* linked this to https://www.nytimes.com/2023/06/09/health/puberty-blockers-transgender-children-britain-nhs.html
[10] *The New York Times* linked this to https://www.socialstyrelsen.se/om-socialstyrelsen/pressrum/press/uppdaterade-rekommendationer-for-hormonbehandling-vid-konsdysfori-hos-unga/

> affirming hormone treatment for those under 18 currently outweigh the possible benefits."

20. The systematic review by Sweden's national health care system has now been published in English as a peer-reviewed article:

> Ludvigsson, J. F., Adolfsson, J., Höistad, M., Rydelius, P.-A., Kriström, B., & Landén, M. (2023). A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica.* doi: 10.1111/apa.16791

As its key points, the review concluded:[11]

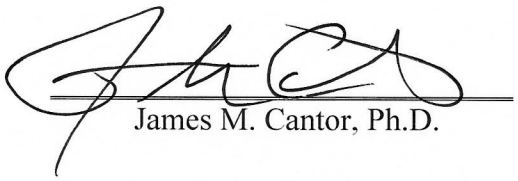
- This systematic review assessed psychosocial effects, bone health, body composition and metabolism, and therapy persistence in children (<18 years of age) with gender dysphoria undergoing treatment with gonadotropin-releasing hormone analogues (GnRHa).
- Long-term effects of hormone therapy on psychosocial health are unknown. GnRHa treatment delays bone maturation and gain in bone mineral density.
- GnRHa treatment in children with gender dysphoria should be considered experimental treatment of individual cases rather than standard procedure.

(The version of this systematic review that was available online was removed when the peer reviewed version became available, which is why Dr. Antommaria was unable to access it, as he indicated in his rebuttal declaration, ¶29.)

21. Appended to this report is the certified translation of Finland's policy on the medical treatment for gender dysphoric minors upon which I relied.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on 8 August 2023 .



James M. Cantor, Ph.D.

[11] Available from https://onlinelibrary.wiley.com/doi/10.1111/apa.16791

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LIST OF APPENDICES

Appendix 1

PRISMA Guidelines

Appendix 2

Certification of official translation

Appendix 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Appendix 2

Lingua Franca Translations

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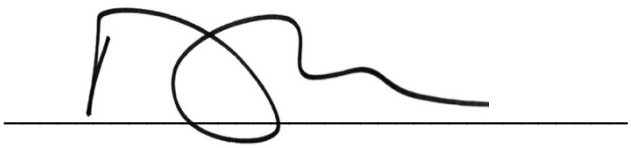
May 18, 2022

CERTIFICATE OF TRANSLATION

Finnish > English > Proofreading of the document titled:

- Recommendation by the Board for Selection of Choices for Health Care in Finland (PALKO / COHERE Finland)

I, Diana M. Arbeláez, with the ATA nr. 251348 at Lingua Franca Translations do hereby certify that the translation herein was completed in accordance with the American Translators Association Code of Professional Conduct and Business Practices and that to the best of my knowledge the translation and proofreading into English herein provided is, in fact, a literal and true interpretation of the statements in the original language Finnish. Under penalties of perjury, I declare that I have read the foregoing document and that the facts stated in it are true.



Diana M. Arbeláez
State of Florida
County of Miami-Dade

STM038:00/2020

Recommendation by the Board for Selection of Choices for Health Care in Finland (PALKO / COHERE Finland)

Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors

Concepts

Suppression treatment	Pubertal suppression with GnRH analogues (drugs that inhibit gonadotropin-releasing hormone activity) to halt the development of secondary sex characteristics of the biological sex.
Cisgender/Cis person	A person whose gender identity matches the sex determined at birth (identifies, and is satisfied with, the sex determined at birth and generally expresses his/her gender accordingly).
Other gender identity	A person who does not identify as a man or a woman, but rather somewhere along the continuum or outside of it; genderless, nonbinary, or multigendered.
Transgender	A person whose gender identity differs from the legal and biological sex determined at birth but instead aligns with the opposite sex.

STM038:00/2020

Content

1. Criteria for Preparation of these Recommendations

As the number of patients, including minors, referred to the Helsinki University Hospital (HUS) and the Tampere University Hospital (TAYS) multidisciplinary outpatient clinics for assessment and treatment of gender dysphoria has increased, PALKO (Council for Choices in Healthcare in Finland / COHERE Finland) decided to prepare recommendations for medical treatments of gender dysphoria, i.e., distress which is associated with a minor's gender variance and impairs function. Gender variance refers to a spectrum of gender experience anywhere on the male-female identity continuum or outside it, and is not exclusively confined to the dichotomized male/female conception of gender. Not all patients with gender variance experience significant suffering or functional impairments, and not all seek medical treatment.

These recommendations are based on the legislation in force at the time of the adoption of the recommendation, the available research evidence, and the clinical experience of multidisciplinary teams with expertise in gender dysphoria assessment and treatment at HUS and TAYS. The knowledge base supporting these recommendations is detailed in a separate Preparatory Memorandum and appendices and includes a description of planning and implementation of medical treatments, a literature review of medical treatments, an extensive ethical analysis, and feedback following meetings with patients and the advocacy groups who represent them.

Finnish legislation defines the requirements for the legal gender recognition of transsexuals (Act on Legal Recognition of the Gender of Transsexuals (Trans Act) 536/2002). The detailed requirements for providing the assessment and treatment to enable legal gender recognition are spelled out further in a Decree of the Ministry of Social Affairs and Health (1053/2002). The Trans Act and the related Decree apply to adults. For those who are not of legal age, there are no laws governing the provision and needs of transgender healthcare; however, these are subject to the Health Care Act of Finland (1326/2010), in particular section 7 (criteria for integrated care), section 7a (criteria for treatment options), section 8 (evidence-based, high quality, safe and appropriate care) and section 10 (rationale for centralization); and also to the Constitution of Finland (731/1999)'s section 6 on equality and section 19 on the right to adequate social and healthcare services. Finland's Act on the Status and Rights of Patients, (785/1992), and especially sections 5, 6, and 7, are also relevant.

2. Target Population - Recommendations

These recommendations apply to minors suffering from dysphoria related to gender variance who are seeking a consultation regarding an evaluation of medical examination and treatment needs; the children and adolescents may identify with the opposite sex (transgender), or may identify as genderless, non-binary, or anywhere along or outside the male/female gender identity continuum (other gender).

3. Assessed Methodology

These recommendations focus on medical treatment procedures that aim to decrease suffering and functional impairment of gender-dysphoric minors.

4. Current Care

Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty. However, in some cases, it persists or even intensifies. Gender dysphoria may also emerge or intensify at the onset of puberty. There is considerable variation in the timing of the onset of puberty in both sexes. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.

Consultation appointments (for parents / caregivers) regarding pre-pubescent children's cross-sex identification or gender dysphoria are provided by the research group on the gender identity of minors at TAYS or HUS. However, ongoing support or other treatment of psychiatric disorders are provided through the local municipal services.

In clear cases of pre-pubertal onset of gender dysphoria that intensified during puberty, a referral can be made for an assessment by the research group at TAYS or HUS regarding the appropriateness for puberty suppression. If no contraindications to early intervention are identified, pubertal suppression with GnRH analogues (to suppress the effect of gonadotropin-releasing hormone) may be considered to prevent further development of secondary sex characteristics of the biological sex.

Adolescents who have already undergone puberty, whose gender dysphoria occurs in the absence of co-occurring symptoms requiring psychiatric treatment, and whose experience of transgender identity failed to resolve following a period of reflection, can be referred for assessment by the research group on the gender identity of minors at TAYS or HUS. Hormone therapy (testosterone/estrogen and anti-androgen) can be started after the diagnostic evaluations, but no earlier than age 16. Additionally, patients under 18 receive three to six months of GnRH analogue treatment prior to the initiation of cross-sex hormones in order to suppress the hormonal activity of the gonads. No gender confirmation surgeries are performed on minors.

5. Risks, Benefits and Uncertainty

The literature review identified two studies with the total of 271 persons diagnosed with childhood-onset gender identity disorder and associated gender or body dysphoria that intensified after the onset of puberty (Preparatory Memorandum Appendix 1, Tables 15 and 16, pages 46-48).

In a smaller study of 70 adolescents, puberty was suppressed with the GnRH analogue at the average age of 14.8 (12-18 years) and puberty blockade continued for an average of 2 years. During the treatment period, the adolescents' mood improved, and the risk of behavioral disorders diminished, but gender dysphoria itself did not diminish, and there were no changes in body image. In a larger study consisting of 201 adolescents, 101 patients with the average age of 15.5 (12-18 years) started an 18-month psychological supportive intervention, and, additionally at six months, pubertal development was suppressed by starting GnRH analogue treatment. The other cohort of 100 only received psychological supportive intervention for 18 months. In both groups, statistically significant increases in global psychosocial functioning were found at 12 and 18 months; among those having received psychological intervention alone, the improvement in global functioning was already significant at the 6-month mark. Both studies lack long-term treatment follow-up into adulthood.

A recent Finnish study, published after the completion of this literature review, reported on the effect of initiating cross-sex hormone therapy on functioning, progression of developmental tasks of adolescence, and psychiatric symptoms. This study found that during cross-sex hormone therapy, problems in these areas did not decrease.

Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system. In trans girls, early pubertal suppression inhibits penile growth, requiring the use of alternative sources of tissue grafts for a potential future vaginoplasty. The effect of pubertal suppression and cross-sex hormones on fertility is not yet known.

6. Ethical Assessment

Although the ethics analysis did not systematically address the issues pertaining to children and adolescents, they have been discussed in several areas in the related documents (Preparatory Memorandum pages 52-62; Appendix 5).

According to the Health Care Act (section 8), healthcare services must be based on evidence and recognized treatment and operational practices. As far as minors are concerned, there are no medical treatment that can be considered evidence-based. At the same time, the numbers of minors developing gender dysphoria has increased. In this situation, it is vital to assure that children and young people are able to talk about their feelings, and that their feelings are acknowledged. The opportunity to reflect on one's experience should be easily accessible through the local health system (i.e., school or student health care, primary care). A young

person's feelings should not be interpreted as immediately requiring specialized medical examinations or treatments.

In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development.

From the point of view of patient advocacy groups, halting puberty is providing young people with a period of reflection, rather than consolidating their gender identity. This is based on the premise that halting the development of one's permanent sex characteristics will improve the minor's social interactions, while allowing more time for diagnostic evaluations. Additionally, patient advocacy groups assert that early intervention with hormonal treatments will lead to improved outcomes for the patients who do eventually pursue gender reassignment. Professionals, for their part, consider it important to ensure that irreversible interventions, which may also have significant adverse effects, both physical and mental, are only performed on individuals who are able to understand the permanence of the changes and the potential for harm, and who are unlikely to regret such interventions. It is not known how the hormonal suppression of puberty affects young people's judgement and decision-making.

The Act on the Status and Rights of Patients (1992/785) states that the patient shall be provided with information about his/her state of health, the significance of the treatment, various alternative forms of treatment and their effects, and about other factors concerning treatment that have an effect on treatment decision-making. In a situation where a minor's identification with the opposite sex causes long-term and severe dysphoria, it is important to make sure that he/she understands the realistic potential of gender reassignment treatments to alter secondary sex characteristics, the reality of a lifelong commitment to medical therapy, the permanence of the effects, and the possible physical and mental adverse effects of the treatments. Although patients may experience regret, after reassignment treatments, there is no going back to the non-reassigned body and its normal functions. Brain development continues until early adulthood – about age 25, which also affects young people's ability to assess the consequences of their decisions on their own future selves for rest of their lives.

A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options.

For children and adolescents, these factors are key reasons for postponing any interventions until adulthood.

7. Conclusions

The first-line intervention for gender variance during childhood and adolescent years is psychosocial support and, as necessary, gender-explorative therapy and treatment for comorbid psychiatric disorders. Uncertainty related to gender identity should be dealt with according to the severity of symptoms and the need for treatment and should be handled at the school / student health care, primary health care at the local level, or in specialty care.

In adolescents, psychiatric disorders and developmental difficulties may predispose a young person to the onset of gender dysphoria. These young people should receive treatment for their mental and behavioral health issues, and their mental health must be stable prior to the determination of their gender identity.

Clinical experience reveals that autistic spectrum disorders (ASD) are overrepresented among adolescents suffering from gender dysphoria; even if such adolescents are presenting with gender dysphoria, rehabilitative interventions for ASD must be properly addressed.

In light of available evidence, gender reassignment of minors is an experimental practice. Based on studies examining gender identity in minors, hormonal interventions may be considered before reaching adulthood in those with firmly established transgender identities, but it must be done with a great deal of caution, and no irreversible treatment should be initiated. Information about the potential harms of hormone therapies is accumulating slowly and is not systematically reported. It is critical to obtain information on the benefits and risks of these treatments in rigorous research settings.

At a minimum, a consultation for a pre- pubescent child at the specialist setting at the TAYS includes an extensive assessment appointment costing EUR 369. If necessary, a day-long outpatient consultation can be arranged, costing EUR 1,408.

The consultation and assessment process for minors at the specialist settings of TAYS or HUS costs EUR 4,300. If it is determined that this process would be untimely, the minimum cost is EUR 640. An initial assessment / consultation by phone costs EUR 100.

The planning and monitoring costs for pubertal suppression are EUR 2,000 for the first year, and EUR 1,200 for subsequent years. The costs for the planning and monitoring of hormone treatments are a minimum of EUR 400 per year.

These costs do not take into account the additional costs of psychosocial support provided in the local level, the possible need for psychiatric treatment, or hormone treatment medication costs.

8. Summary of the Recommendations

PALKO / COHERE maintains the following:

1. For the treatment of gender dysphoria due to variations in gender identity in minors, psychosocial support should be provided in school and student healthcare and in primary healthcare, and there must be sufficient competency to provide such support.
2. Consultation with a child or youth psychiatrist and the necessary psychiatric treatment and psychotherapy should be arranged locally according to the level of treatment needed.
3. If a child or young person experiencing gender-related anxiety has other simultaneous psychiatric symptoms requiring specialised medical care, treatment according to the nature and severity of the disorder must be arranged within the services of their own region, as no conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.

PALKO / COHERE considers that the consultation, periods of assessment, and treatments by the research group on the gender identity of minors at TAYS or HUS must be carried out according to the following principles:

1. Children who have not started puberty and are experiencing persistent, severe anxiety related to gender conflict and/or identification as the other sex may be sent for a consultation visit to the research group on the gender identity of minors at TAYS or HUS. Any need for support beyond the consultation visit or need for other psychiatric treatment should be addressed by local services according to the nature and severity of the problem.

2. If a child is diagnosed prior to the onset of puberty with a persistent experience of identifying as the other sex and shows symptoms of gender-related anxiety, which increases in severity in puberty, the child can be guided at the onset of puberty to the research group on the gender identity of minors at TAYS or HUS for an assessment of the need for treatment to suppress puberty. Based on these assessments, puberty suppression treatment may be initiated on a case-by-case basis after careful consideration and appropriate diagnostic examinations if the medical indications for the treatment are present and there are no contraindications. Therapeutic amenorrhea, i.e. prevention of menstruation, is also medically possible.

3. A young person who has already undergone puberty can be sent to the research clinic on the gender identity of minors at TAYS or HUS for extensive gender identity studies if the variation in gender identity and related dysphoria do not reflect the temporary search for identity typical of the development stage of adolescence and do not subside once the young person has had the opportunity to reflect on their identity but rather their identity and personality development appear to be stable.

4. Based on thorough, case-by-case consideration, the initiation of hormonal interventions that alter sex characteristics may be considered before the person is 18 years of age only if it can be ascertained that their identity as the other sex is of a permanent nature and causes severe dysphoria. In addition, it must be confirmed that the young person is able to understand the significance of irreversible treatments and the

benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present.

5. If a young person experiencing gender-related anxiety has experienced or is simultaneously experiencing psychiatric symptoms requiring specialized medical care, a gender identity assessment may be considered if the need for it continues after the other psychiatric symptoms have ceased and adolescent development is progressing normally. In this case, a young person can be sent by the specialized youth psychiatric care in their region for an extensive gender identity study by the TAYS or HUS research group on the gender identity of minors, which will begin the diagnostic studies. Based on the results of the studies, the need for and timeliness of medically justified treatments will be assessed individually.

Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors. The initiation and monitoring of hormonal treatments must be centralized at the research clinics on gender identity at HUS and TAYS.

9. Additional Evidence Gathering and Monitoring the Effectiveness of Recommendations

Moving forward, the following information must be obtained about the patients diagnosed and receiving treatments in Finland before re-evaluating these recommendations:

- Number of new patient referrals
- Number of patients starting the assessment period, and numbers of new transgender (F64.0) vs “other gender” (F64.8) diagnoses
- Whether the diagnosis remains stable or changes during the assessment phase
- Number of patients discontinuing the assessment period and the reasons for the discontinuation
- Adverse effects of treatments (especially long-term effects and effect on fertility)
- Number of patients regretting hormone therapy
- Analysis of the effects of the assessment and the treatment period on gender dysphoria outcomes, as measured by the Gender Congruence and Life Satisfaction Scale (GCLS)
- Analysis of the effects of the assessment and the treatment period on functional capacity and quality of life
- The prevalence of co-occurring psychiatric diagnoses (especially neurodevelopmental diagnoses F80-F90) among those diagnosed with / seeking treatment for gender dysphoria, and whether the presence of these co-occurring diagnoses impacts the ability to achieve the desired outcome (e.g. decreased dysphoria) in the assessment or the treatment phase.
- Whether the assessment and treatment periods lead to a reduction of suicide attempts
- Whether the assessment and treatment periods lead to a reduction in depression and distress

10. Attachments

Preparatory Memorandum, with Appendices 1-5.